doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,354,844 (herein the '844 patent - formerly U.S. Application Serial No. 07/492,460) in view of Wu *et al.*, U.S. Patent No. 5,166,320 (herein "Wu"), Knapp *et al.*, *Immunology Today 10*(8):253-258 (1980) (herein "Knapp"), Goers *et al.*, U.S. Patent No. 4,867,973 (herein, "Goers"), Hirsch *et al.*, U.S. Patent No. 5,428,132 (herein "Hirsch") and Rossi *et al.*, U.S. Patent No. 5,114,019 (herein, "Rossi"). Applicants respectfully traverse this rejection and incorporate by reference herein, reiterate, and expand upon the response filed November 29, 1994.

Specifically, in paragraph 16 of the Office Action, the Examiner states, that:

> [O]ne of ordinary skill in the art would recognize that where the introduction of nucleic acids, such as ribozymes, into T cells is desired, one of ordinary skill would necessarily utilize proteins, such as gp120 or antibodies to T-cell proteins known to be capable of initiating endocytosis, in order to facilitate the introduction of DNA into the target cells, especially in view of the Hirsch *et al.* patent which specifically suggests the use of antibodies to target DNA to T-cells for the purposes of transformation or to introduce exogenous DNA sequences into the cells . . .

This is then concluded with "[i]n view of the teachings of the references, it would have been prima facie obvious to one of ordinary skill in the art to substitute antibodies for the transferrin-targeting agent of the '844 patent." Applicants respectfully disagree.

The Federal Circuit has clearly stated that "the law of double patenting is concerned *only* with what patents *claim*. 'Double patenting,' therefore, involves an inquiry into what if anything, has been claimed twice." *General Foods Corp. v. Studiengesellschaft KmbH*, 23 U.S.P.Q.2d 1839, 1840 (Fed. Cir. 1992) (Emphasis in original.) Applicants assert that nothing is being claimed twice, nor are applicants merely claiming an obvious variation of the invention set forth in the claims of the '844 patent. Therefore, the double-patenting rejection is incorrect.

Further, the court clearly indicated the necessity of comparing *only* the claims in the application rejected on obviousness-type double patenting. In particular, it was stated that "[w]e are not here concerned with what one skilled in the art would be aware [of] from *reading* the claims but with what inventions *the claims define*." *Id* at 1846 *citing In re Sarett,* 140 U.S.P.Q. 474, 481 (C.C.P.A. 1964) (Emphasis in original). Based on such an analysis, Applicants continue to maintain that the claims of the invention are not rendered obvious by the claims of the '844 patent even in view of the art applied by the Examiner, and therefore there is no obviousness-type double patenting.

Addressing the specific points raised in the Office Action of February 28, 1996, the Applicants continue to maintain, as previously stated at page 4 of the November 29, 1994 response, that the Examiner has presented no evidence based upon the prior art why one "would recognize" that it would be "necessary" to utilize proteins such as gp120 or antibodies to T-cell proteins in the claimed invention. He has merely stated his own opinion that such is the case.

The Examiner has further attempted to bolster this argument by the addition of Hirsch. Nowhere, however, does Hirsch *et al.* discuss the use of "protein-polycation conjugates." Hirsch refers only to a DNA-antibody conjugate with direct linkages between the DNA and antibody (column 2, lines 15-20) as a method for integration of foreign DNA into cells. Contrary to this, the claimed conjugates have an indirect linkage, i.e.through the polycation complex. Thus, regardless of whether Hirsch refers to transfection or "antifection" of T-lymphocytes using an antibody against T-cells, this still fails to render obvious the claims of the invention in view of the '844 patent and the combination of the applied art.

Additionally, the ligands used by Wagner or Wu are ligands whose physiological function is endocytosis. The person skilled in the art would not expect that substitution of antibodies in the conjugates of polycations and proteins having naturally endocytotic activity would work. Therefore, it would *not* have been obvious to expect that antibodies, whose physiological function is distinct from that of proteins known to cause endocytosis, could when coupled to a polycation, be utilized to efficiently internalize DNA such that it will be expressed in the cell.

As previously indicated at page 4, first full paragraph, in the response filed November 29, 1994,

> Further, and more seriously, the Examiner has failed to provide any reason whatsoever in the cited art why one of skill in the art would even want to introduce the nucleic acids into T-cells. Therefore, the Examiner is premising the rejection on the conclusion that one would have a reason to introduce nucleic acids such as ribozymes into T-cells. Thus, the rejection is based on conclusory arguments having no basis in the cited art.

The Examiner has still failed to address this argument in the current Office Action. Merely because the Examiner recites that "one of ordinary skill in the art would recognize that where the introduction of nucleic acids. . . is desired,. . . one would necessarily utilize proteins. . ." this does not address the issue. This is because the Examiner *presupposes* the desire to introduce the nucleic acids into the T-cells, rather than providing a motivation in the applied art for doing so. Applicants respectfully request the Examiner to respond to the above argument in the next action.

Applicants still maintain that given the large number of possible results that one might obtain by combining the art applied by the Examiner with the claims of the '844 patent, and the lack of any motivation to prepare the specifically-claimed conjugates or complexes, the most likely possibility is that one would *not* obtain the claimed invention. It is respectfully suggested that the Examiner is continuing to use hindsight in his analysis of the claimed invention

Certainly, once one knows what the invention is -- as set forth in the filed application -- it is possible that one might then be able to fit together the individual pieces from the applied art and the '844 patent claims. Without the claims of current application in front of the ordinary artisan, however, a myriad of possibilities are obtainable based merely on a combination of the claims of the '844 patent and the applied art.

Based on the above arguments, it is the Applicants' position that the Examiner is in error in making the obviousness-type double patenting rejection. Therefore, the rejection of claims 1-20, 28-29, 32-34 and 36-40 should be withdrawn.

III. Objection to the Specification and Rejection of Claim 38 under 35 U.S.C. § 112, First Paragraph

In the Office Action at paragraph 17, the Examiner objected to the specification and rejected claim 38 under 35 U.S.C. § 112, first paragraph, as allegedly "failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention." Applicants respectfully traverse this rejection.

Specifically, the Examiner contends that "Applicants have not disclosed how to use the claimed compositions, complexes and processes therapeutically in humans. Claims drawn to pharmaceutical compositions are viewed as therapeutic agents." The Examiner then proceeds further, on page 3, to acknowledge that Applicants have in fact provided *in vitro* examples of cellular transfections with the claimed conjugates.

Applicants disagree with the Examiner that the use of the term "pharmaceutical" in claim 38 would always imply or require *in vivo* use. A pharmaceutical preparation has *in vivo* as well as *in vitro* applications. In *in vitro* therapy, a patient's cells, grown outside of his or her body (*ex vivo*), may be treated with the pharmaceutical preparation, and all or some of the treated cells may be returned to the patient's body to ameliorate a disease or a medical condition. Such preparation should still be characterized as a pharmaceutical preparation. As admitted by the Examiner, the Applicants have demonstrated *in vitro* activity (page 3, second full paragraph). Therefore, Applicants have shown how to use the pharmaceutical preparation of claim 38.

At page 3, paragraph A, the Examiner refers to *Ex parte Forman*, 230 U.S.P.Q. 546 (B.P.A.I. 1986). In citing the case law, the Examiner states that "factors to be considered in determining *scope and enablement* are . . ." and then proceeds to list a number of factors which were set forth in *Forman*. Applicants respectfully draw the Examiner's attention to page 547, right hand column, last full paragraph, of the decision where *Forman* states "the determination of what constitutes *undue experimentation* in a given case requires the application of a standard of reasonableness . . ." *Forman* then proceeds to list the factors which the Examiner has enumerated. As such, the Examiner's legal basis for this rejection appears to be incorrect since he refers to "scope and enablement," not "undue experimentation" and thereafter recites the *Forman* factors. Furthermore, even if the Examiner really intended to assert that "undue experimentation" was required to enable the claimed invention, the rejection is still incorrect because the Examiner has failed to indicate where or why such "undue experimentation" would be necessary. Therefore, *Forman* is improperly cited in the Examiner's rejection and is not relevant to the rejection as set forth.

Concerning the Examiner's reference to the *Washington Post*, December 1995, Applicants assume the Examiner is referring to the article entitled "Gene Therapy 'Oversold' by Researchers, Journalists" in the December 8, 1995 issue of the paper. First, merely because something is alleged to be unpredictable, this does not preclude enablement. Second, the Examiner has failed to point to any reference to the claimed invention's *lack* of potential use in gene therapy and therefore it is Applicants' position that the article is not relevant to the rejection of claim 38. Additionally, as indicated above, the pharmaceutical composition of the claimed invention should not be limited to *in vivo* use.

Next, the Examiner argues that, "Applicant's [sic] compositions and processes do not utilize targeting agents which would be recognized as self by the human immune system. The invention appears to rely on the use of murine monoclonal antibodies . . ." Despite the fact that Applicants have exemplified the claimed invention using murine monoclonal antibodies, this does not preclude the use of other "self-recognized" antibodies as deemed appropriate. In other words, Applicants' claims are not limited to the use of murine antibodies for targeting the protein-polycation conjugate.

Clearly one of skill in the art would, as deemed necessary, replace such murine antibodies with either humanized or actual human antibodies obtained by recombinant techniques (See specification at page 11, second full paragraph) if prolonged *in vivo* use was expected. Alternatively, there is no reason that a human anti-mouse antibody response might not be avoided if such antibodies were used only once or a few times. Similarly, this argument also applies to the Examiner's concerns about gp 120 provoking an immune response. The law does not require that an invention be useful more than once with a particular patient.

Finally, at page 3, fourth line from the bottom, the Examiner indicates that "chloroquine is required to transfect cells in *some* instances." (Emphasis added). He then attempts to use this as an argument for non-enablement based on chloroquine's alleged cytotoxicity. First, the Examiner's use of the term "required" is incorrect, since even where chloroquine was used, transfection was still successful in its absence (e.g. see Figure 3). Second as the Examiner properly noted, chloroquine was *not* even used in all transfections (e.g. see Figures 4 and 5). Therefore, the use of chloroquine is not an absolute requirement and this aspect of the rejection is not relevant.

Finally, at the beginning of the rejection (page 3, line 1), the Examiner also based the rejection on "failing to present the best mode contemplated. . ." Applicants respectfully disagree. Because the Examiner has failed to provide any additional specifics in this regard, however, Applicants respectfully request additional elaboration on this aspect of the rejection in the next Office Action, at which time, if necessary, they will respond in detail.

Therefore, based on the above arguments the objection to the specification and rejection of claim 38 is incorrect and should be withdrawn.

IV. Rejection of the Claims Under 35 U.S.C. § 103

A. Rejection of claims 1-8, 11-20, and 36-40

At page 4 of the Office Action, the Examiner maintained the rejection of claims 1-8, 11-20 and 36-40 under 35 U.S.C. § 103 as allegedly being unpatentable over Wu or Wagner *et al.*, *Proc. Natl. Acad. Sci. USA 87*:3410-3414 (1990), - herein "Wagner") in view of Goers *et al.* or

Hirsch, Carriere and Knapp. Applicants respectfully traverse this rejection, incorporate by reference herein, reiterate and expand upon the response filed November 29, 1994.

At paragraph 18, line 19, the Examiner acknowledges that the references "do not teach the use of T-cell specific antibodies for the targeting of polycation nucleic acid complex in the cells." The Examiner then proceeds at page 5, beginning with line 3, to set forth the specifics of the rejection as follows:

> One of ordinary skill in the art at the time the invention was made would have been motivated to select and substitute T-cell specific antibodies or gp120 (for the transferrin molecule of Wu et al or Wagner et al.) as the targeting agents for protein-polycation conjugates or complexes of said conjugates additionally containing nucleic acids because such antibodies would allow for the specific direction and introduction of nucleic acid laden conjugates to T-cells for the purpose of introducing foreign DNA into the cells for either therapeutic purposes or for the production of interleukins. One of ordinary skill in the art would have also been motivated to transfect T-cells through the contacting of T-cell markers with T-cell antibody specific DNA conjugates in o [sic] From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants respectfully disagree.

Applicants have previously addressed the points raised by the Examiner as they relate to the applied art in the responses filed March 11, 1994 and November 29, 1994. These arguments still apply. Therefore Applicants will now address their comments to the Examiners "Response to Traversal" at page 5, paragraph 19 which is stated as follows: "Is Applicant's invention, namely proteins which are able to deliver nucleic acids specifically into T-cells rendered obvious to those skilled in the art based on the combination of references and in view of the skill level at the time of the invention?" (Paragraph 19, lines 9-12.) The answer is no!

Applicants first wish to point out what appears to be a mis-statement on the part of the Examiner. As recited above, the Examiner refers to "Applicant's invention, namely proteins which are able to deliver nucleic acids . . . " Applicants' invention is not merely drawn to a protein that is able to deliver nucleic acids into a T-cell, but rather, as clearly set forth in the claims to *inter alia*, "a protein-polycation conjugate capable of forming, with nucleic acids or nucleic acid analogues, soluble complexes which are adsorbed. . . ." It is respectfully suggested that the Examiner's analysis, if it is based solely upon a consideration of the invention being proteins able to deliver nucleic acids, unduly simplifies the issue. This type of error in the analysis of the invention (i.e. piece by piece) has previously been pointed out in the response of November 29, 1994 at pages 14-15.

Applicants continue to maintain that the Examiner is in effect taking the teachings of the applied art and attempting to combine them to arrive at the claimed invention without any suggestion to do so (in either the art or in the body of knowledge which one of skill in the art might be expected to possess). Applicants again respectfully request the Examiner to provide a motivation to combine the references to obtain the claimed invention. As previously stated at page 13, lines 11-14 of the last response,

> Simply saying that one of skill in the art would make such a change because a body of knowledge exists to which that individual might have access is not sufficient. There must be a clear reason why such a combination would have been obvious to one of ordinary skill in the art.

Further, even if the Examiner combined the applied art there would *not* be a reasonable likelihood of obtaining the claimed invention. The teachings presented by the Examiner may result in any one of a myriad of possibilities, where only specific combinations might conceivably lead to the claimed invention. In other words, the likelihood of successfully

obtaining the claimed invention by combining the references is low, without any further indication concerning the appropriate direction in which to proceed.

Additionally, at page 15 of the response filed November 29, 1994, Applicants requested the Examiner to specifically indicate how Wagner might be used in conjunction with the additional applied art to obtain the claimed invention, because Wagner refers to his delivery system as useful for "Transferrinfection" and as such clearly only contemplated one use for such a system. Wagner's system deliberately takes advantage of the ubiquitous expression on cells of the transferrin receptor. The binding to a transferrin receptor is excluded from the claimed invention. The Examiner appears to have overlooked Applicants' previous request and is again respectfully requested to respond.

Additionally, at pages 15-16 of the same response, Applicants argued that Carrier "discloses internalization of monoclonal antibody-gold-antigen complexes" which is distinct from the claimed invention, and that such results appeared to direct the investigator solely to the use of ligand-gold conjugates (e.g., see page 125, line 36, where it is stated that "This validates the use of ligand-gold conjugates"). No rebuttal of this argument was presented by the Examiner.

In the Office Action at page 5, lines 15 of Paragraph 19, the Examiner refers to "Applicants' admitted prior art Zon *et al.*, especially pages 545-546." Applicants have not, to their knowledge, acknowledged that Zon *et al.* is in fact prior art to the claimed invention. Further, it is not clear to Applicants where in the specification the Examiner is referring. Applicants respectfully request the Examiner to clearly point out the reference to Zon *et al.* to which he is referring. Additionally, Applicants respectfully request the Examiner to more

specifically cite Calliere *et al.* (Paragraph 19, line 17) to allow Applicants the appropriate opportunity to respond.

The use of Hirsch has previously been addressed at page 3 of this response, and the same comments are applicable to this rejection.

Finally, the Examiner refers to *In re McLaughlin,* 170 U.S.P.Q. 209 (C.C.P.A. 1974) in an attempt to assert a justification for his "hindsight reasoning." The key part of this cite as correctly set forth by the Examiner is that such reasoning "does not include knowledge gleaned *only* from the Applicants' disclosure. . ." (Emphasis added.) It is this prohibition which the Examiner has violated, because it is only with the "roadmap" provided in Applicants' disclosure that one would be able to take the unrelated bits and pieces found in the art and combine them to obtain the claimed invention. Without such information from the disclosure, the possibilities which one might arrive at are too numerous to provide a reasonable expectation of successfully obtaining the claimed invention.

Therefore, based on the above arguments the rejection of claims 1-8, 11-20 and 36-40 under § 103 are incorrect and should be withdrawn.

B. Rejection of claims 17, 20, 28-29 and 32-34

At page 6, paragraph 20, the Examiner rejected claims 17, 20, 28-29 and 32-34 as allegedly being unpatentable over Wu or Wagner in view of Goers, Hirsch, Knapp and Carriere as applied in the previous rejection and further in view of Haseloff *et al., Nature 334*:585-591 (1988) (herein "Haseloff") or Rossi *et al.*, U.S. Patent No. 5,144,019 (herein "Rossi"). Applicants

respectfully traverse this rejection and incorporate by reference herein, reiterate and expand upon the Response filed November 29, 1994.

Specifically, in the Office Action beginning at Paragraph 20, line 31, the Examiner stated that:

> In view of the teachings of Rossi *et al.* and/or Haseloff *et al.*, one of ordinary skill would have recognized that the targeting of ribozymes to T-cells expressing oncogene proteins or HIV proteins using polycation-protein conjugates such as those taught by Wagner *et al.* would have been useful for inactivation of the genetic transcripts contained within the cells. Further, one of ordinary skill would have recognized, prior to Applicant's earliest priority date, that the targeting specificity of the system disclosed by Wagner *et al.*could be greatly enhanced by the use of antibodies to specifically target therapeutic agents such as ribozymes.
>
> One of ordinary skill in the art at the time the invention was made would have been motivated to select and substitute T-cell specific antibodies or gp120 (for the transferrin molecule of Wu *et al.* or Wanger *et al.*) as the targeting agents for protein-polycation conjugates or complexes of said conjugates additionally containing nucleic acids because such antibodies would allow for the specific direction and introduction of ribozyme laden conjugates to T-cells for the purpose of introducing foreign nucleic acids, such as ribozymes, into the cells for the inactivation of RNA contained with the cells. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The specific problems with the applied art have previously been presented in the Responses filed March 11, 1994 and November 29, 1994. These apply equally well to the current rejection. Therefore, the Applicants will only specifically address the Examiner's "Response to the Traversal" at paragraph 21 on page 7 of the Office Action. The Examiner's "Response"

beginning at Paragraph 21, line 15 can be summarized as follows:

> In view of the combined references, it is the conclusion of the Examiner that one could reasonably expect to arrive at the claimed invention because those skilled in the art recognized the usefulness of introducing ribozymes into target cells and also recognized and knew those antibodies useful in targeting materials into T-cells. The construction of proteins[sic]-polycation conjugates according to the claimed invention was within the skill level of the routineer and one of ordinary skill would have been motivated to construct such products because they would have been useful for the introduction of nucleic acids into cells in a manner directly analogous to that of Wu *et al.*or Wagner *et al.*

The problem with the basic combination of applied art, i.e. the combination without Haseloff or Rossi has been addressed in the immediately preceding rebuttal. These arguments are equally applicable to this rejection. Haseloff and Rossi fail to remedy the deficits of the initial combination. Further, the use of Haseloff and Rossi is nothing more than an attempt to add components previously missing from the combination in an attempt to arrive at the claimed invention. As has been repeatedly argued, such picking and choosing pieces from the art, without any suggestion or motivation to do so is an improper approach to the obviousness analysis.

Further, the Examiner continues to rely upon the conclusion that the basis for the combination of the references is that "those skilled in the art recognize the usefulness of introducing ribozymes in the target cells. . ." This is phrased somewhat differently than in the previous rejection as "[t]he 'anti-gene activity' of ribozymes is indicated to provide a basis for gene therapy of various diseases. . ." (Paragraph 20, lines 17-18) and that the motivation to construct such products was that "they would have been useful for inactivation of the genetic transcripts contained within the cells." (Paragraph 20, lines 34-35). Finally in Paragraph 21, lines 16-18, the Examiner's basis for a reasonable expectation of success of obtaining the

claimed invention is that "one could *reasonably expect to arrive* at the claimed invention *because* those skill in the art *recognized the usefulness* of introducing ribozymes into target cells and also recognized and knew those antibodies useful in targeting materials into T-cells." (lines 16-18). (Emphasis added). Clearly, the Examiner has improperly attempted to base both the motivation or suggestion for combining the art as well as the reasonable expectation of successfully of obtaining the claimed invention on the "recognized usefulness" of what is *only* disclosed in Applicants' specification. Applicants again reiterate that *both* a motivation to combine the references and a reasonable expectation of successfully obtaining the claimed invention after combining the references are necessary to establish a *prima facie* case of obviousness *In re* Vaeck 20 U.S.P.Q. 1438, 1442 (Fed. Cir. 1991). These must be present before combining the art, not after one has already decided what they wish the combination of art to show. Neither of these are found in the Examiner's bases for combining the art as set forth in the Examiner's rejections. Therefore, based on the above arguments, the Applicants continue to maintain that the Examiner has failed to establish a *prima facie* case of obviousness and that the rejection of claims 17, 20, 28-29 and 32-34 should be withdrawn.

C. Rejection of claims 1 and 9-10

At page 8, paragraph 22, the Examiner has rejected claims 1 and 9-10 under 35 U.S.C. § 103 as allegedly being unpatentable over Wu or Wagner in view of Goers and Knapp and Carriere and further in view of newly cited Goding *et al., J. of Immun. Meth. 20*:241-253 (1978) (herein "Goding"). Applicants respectfully traverse this rejection.

At page 8, the Examiner acknowledges that the teaching of the art at least "differ[s] from the claimed invention in that the binding attachment of polycation to antibody through protein A-antibody interaction is not taught in the combination of references". He then proceeds to assert that Goding teaches that protein A may be used as an immunological reagent to attach reagents to antibody molecules. Specifically, at paragraph 22, lines 18-26, the Examiner asserts that:

> One of ordinary skill in the art at the time the invention was made would have been motivated to select make [sic] an antibody-protein A-polycation compound because such proteins would have allowed for the specific direction and introduction of nucleic acid laden conjugates to T-cells or facilitated the isolation of such antibodies through ion exchange chromatography. From the teachings of the references, it is apparent that one of ordinary skill in the art would have a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Goding adds nothing to the already rebutted combination of the art that would remedy the deficits in said art. Goding does nothing more than provide information on the general feature of protein A as an immunological reagent. As such, it does nothing, however, to suggest a combination of the art which would result in obtaining the claimed invention.

Again, the Examiner has done no more than merely taken an isolated component of the invention, which may be found in the art. The invention must be considered as a whole (not as isolated components). This has already been argued, earlier in this response, as an inappropriate approach for obtaining the claimed invention. Therefore this rejection of claims 1 and 9-10 is incorrect and should be withdrawn.

Applicants respectfully request the reconsideration and re-examination of this application and the timely allowance of the pending claims. If there are any other fees due in connection with the filing of this Response, please charge the fees to our Deposit Account 19-0036. If a fee

is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should be charged to our Deposit Account.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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